A randomized multicenter phase II trial on the efficacy of a hydrocolloid dressing containing ceramide with a low-friction external surface for hand-foot skin reaction caused by sorafenib in patients with renal cell carcinoma†

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Background: The purpose of this study was to investigate the usefulness of a hydrocolloid dressing containing ceramide for hand-foot skin reaction (HFSR) on the soles of the feet in metastatic renal cell carcinoma (RCC) patients treated with sorafenib.

Patients and methods: Patients with grade 1 HFSR on the soles of the feet were randomly assigned in to two groups. One group received a hydrocolloid dressing containing ceramide (arm A) and the other received 10% urea cream (arm B). Patients in both groups applied treatment to the affected sites on the soles of the feet, but not to the hands. The primary end point was the incidence of grade 2 or 3 HFSR on the soles of the feet in the first 4 weeks.

Results: Thirty-three patients were assessed (17 in arm A and 16 in arm B), and there were no significant differences in baseline characteristics between the two groups. During the observation period of this study, grade 2 or 3 HFSR on the soles of the feet was found in 29% of patients in arm A and was significantly less than the 69% in arm B (P = 0.03). The incidence of HFSR on the hands, however, was similar in both arms. The median time to grade 2 or 3 HFSR on the soles of the feet was also significantly longer in arm A than in arm B (P = 0.03).

Conclusions: These results indicate that a hydrocolloid dressing containing ceramide prevented the worsening of HFSR caused by sorafenib in metastatic RCC patients.

Clinical trial registration number: UMIN000002016.

Key words: hand-foot skin reaction, sorafenib, renal cell carcinoma, hydrocolloid dressing, ceramide

introduction

The treatment of metastatic renal cell carcinoma (RCC) has dramatically evolved over time such that drugs like sorafenib and sunitinib, which target specific molecules, have been widely used as standard treatment of metastatic RCC [1]. Despite the clinical effectiveness of these drugs, they are accompanied by several adverse events. Hand-foot skin reaction (HFSR) is the most clinically significant and dose-limiting dermatologic toxicity in metastatic RCC patients treated with sorafenib [2]. In the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study, HFSR was observed in 30% of patients administered sorafenib and most of these patients discontinued the treatment due to adverse events [3]. In a study of 131 Japanese patients, the incidence of all grades of HFSR was reported to be 51% with 7% of patients affected by grade 3 HFSR [4]. As HFSR is associated with significant tenderness, which affects both function and quality of life, the prevention and management of HFSR in metastatic RCC patients taking sorafenib has become a high priority.

Although treatment with topical urea cream is frequently administered to these patients, an evidence-based treatment strategy has not been well established [5]. HFSR is more likely to develop on the soles of feet, which are subjected to relatively high pressures and physical stress [6]. As a hydrocolloid
dressing containing ceramide with a low-friction external surface (Remois pad®, ALCARE Co. Ltd., Tokyo, Japan) has been used to treat pressure ulcers by reducing surface pressure and preventing skin damage [7], this dressing may also be suitable to prevent the development and worsening of HFSR. We thus conducted a prospective randomized open-label trial to investigate the usefulness of a hydrocolloid dressing containing ceramide with a low-friction external surface for HFSR that developed on the soles of the feet in patients administered sorafenib.

patients and methods

study design

This study was a two-arm, multicenter, open-label, randomized phase II clinical trial that evaluated the efficacy of a hydrocolloid dressing containing ceramide with a low-friction external surface versus 10% urea cream to treat HFSR on the soles of the feet in metastatic RCC patients taking sorafenib. The study was conducted at 15 institutes belonging to the Japanese Society of Renal Cancer. Patients were randomly assigned into two equal groups: patients who received a hydrocolloid dressing containing ceramide with a low-friction external surface (arm A) and patients treated with 10% urea cream (arm B). Randomization was achieved by the minimization method and patients were stratified only by gender. The study protocol and informed consent forms were approved by the Institutional Review Board at each participating institute. The trial was conducted in accordance with the Declaration of Helsinki and was registered with the clinical trial registration number UMIN000002016. All patients provided written informed consent.

patients, treatment, and evaluation

Patients with metastatic RCC who developed grade 1 HFSR on the soles of the feet during treatment with sorafenib (400 mg b.i.d.) were enrolled. Eligibility criteria included an Eastern Clinical Oncology Group (ECOG) performance status of 0 or 1; patients aged 20 years or older; histologically confirmed metastatic RCC; and a life expectancy of at least 12 weeks. Patients were excluded if they had been previously treated with other drugs designed against specific molecular targets and had a systemic dermatologic disease, ≥grade 2 HFSR on the hand, or ≥grade 3 adverse events other than HFSR.

Patients assigned to arm A were treated by replacing a hydrocolloid dressing containing ceramide with a low-friction external surface to the affected sites of the foot soles with HFSR every 2–3 days. Patients applied this dressing according to the instruction manual of Remois pad® (www.alcare.co.jp/e). Patients assigned to arm B received 10% urea cream to the affected sites two to three times per day. Other treatments such as topical steroid ointments, painkillers, or foot care products for HFSR on the soles of the feet were prohibited during the study period. Progress of patients was monitored every 2 weeks, and each group was treated for 4 weeks if the grade of HFSR on the soles of the feet had not worsened to grades 2 or 3.

assessments

The primary end point was the incidence of grade 2 or 3 HFSR on the soles of the feet in the first 4 weeks. Secondary end points were the time until the occurrence of grade ≥2 HFSR on the soles, the relative dose intensity of sorafenib, QOL assessments, and adverse events. The relative dose intensity in each patient was calculated by the equation: (actual dose of sorafenib)/(800 mg/day × 28 days) × 100. The actual dose was the cumulative dose between the beginning of the study and the end of the treatment protocol excluding periods where administration was discontinued. We evaluated physical disorders, social disorders, and pain associated with HFSR on the foot soles using a questionnaire with visual analog scales (VAS). All questionnaires were self-administered before the study began and again at 2 and 4 weeks after the beginning of the study. Patients completed the questionnaires and returned them by mail.

statistical methods and analysis

The number of patients necessary for the study was calculated on the basis of the results of phase II trials in Japan [4]. Of the 72 patients who were confirmed to have HFSR, grade 2 or 3 HFSR was observed in 35 patients (∼50%). In the present study, the incidence of grade 2 or 3 HFSR was expected to decrease to ∼25% by using a hydrocolloid dressing containing ceramide with a low-friction external surface. Expecting to utilize Fisher’s exact test with a one-sided α error of 0.05 and β error of 0.2, the necessary number of patients was estimated to be 46 in each group and 92 total patients for two groups. We intended to register 100 patients anticipating that ∼10% would be ineligible or unable to be assessed.

The incidence of grade 2 or 3 HFSR was compared between both groups by Fisher’s exact test. As this study was a phase II trial designed to examine whether the dressing prevents the occurrence of HFSR, one-sided tests were carried out. The time until the occurrence of grade 2 or 3 HFSR on the soles of the feet was calculated by the Kaplan–Meier method and a comparison between the two groups was carried out using the log-rank test. Values of the relative dose intensity were compared by t-tests. Regarding pain assessment, the pain score was compared between the groups using the Wilcoxon rank-sum test. Stata (version 12; Stata Corp., TX) was used for statistical analyses.

results

Owing to the slow accrual of patients, the study was stopped in March 2009 when 36 patients were registered and 18 were assigned to each arm. One patient in each group was determined to be ineligible and an additional patient in arm B developed drug eruptions 1 day after registration without undergoing treatment. Therefore, analyses regarding treatment efficacy include data from 17 patients in arm A and 16 patients in arm B (Table 1). Patient backgrounds were well balanced between the two groups. The number of subjects available for safety analysis was 18 in arm A and 17 in arm B.

Table 2 shows the frequency of the highest grade of HFSR on the soles of feet in patients from each group during the observation period. The incidence of grade 2 or higher HFSR was significantly higher in arm B (P = 0.03) being observed in 11 of 16 patients (68.8%), while only being observed in 5 of 17 patients in arm A (29.4%). Table 3 shows the frequency of patients who developed equally high-grade HFSR on the hand. No significant difference was observed between the two groups (P = 0.58). A significant difference in the median time to onset of grade 2 or 3 HFSR was observed between the groups (P = 0.03). The median time to the onset of grade 2 or 3 HFSR was longer than 28 days for arm A. The lower limit of the 95% confidence interval (95% CI) was 13 days with an upper limit >28 days. For arm B, the median time was 22 days (95% CI 15–27 days) (Figure 1). The duration of sorafenib treatment was 26 ± 6 days in arm A (range: 6–28 days) and 23 ± 7 days (range: 5–28 days) in arm B and was not significantly different (P = 0.134). Compliance with prescribed sorafenib therapy during the study period was observed in 11 of 17 patients (65%) in arm A and 5 of 16 patients (31%) in arm B. The relative dose intensity of sorafenib...
was statistically similar between the two groups \( (P = 0.358) \) and was 82 ± 27% in arm A and 73 ± 26% in arm B.

Of the 33 patients available for efficacy analysis, questionnaires assessing QOL 2 weeks after the start of treatment were received from 15 patients (88%) in arm A and 12 (75%) in arm B. Questionnaires assessing QOL 4 weeks after the start of treatment were received from 11 (65%) patients in arm A and 8 (50%) in arm B. Most items on the QOL assessment were not significantly different between the two groups at any point. However, the mean pain score ‘during the last 7 days’ on the questionnaire administered 4 weeks after the start of treatment was significantly lower for arm A than arm B \( (P = 0.05) \) (Table 4). Regarding adverse events, a mild skin sore was noted in one patient in arm A and no adverse events were observed in arm B.

**discussion**

In this study, we demonstrate that a hydrocolloid dressing containing ceramide with a low-friction external surface is an effective treatment to prevent HFSR on the soles of the feet progressing from grade 1 to 2 or 3 compared with topical 10% urea cream in patients with RCC undergoing sorafenib therapy. Additionally, the time to progression from grade 1 to 2 or 3 was longer with the dressing than with 10% urea cream. The treatment with a hydrocolloid dressing containing ceramide with a low-friction external surface was also effective at reducing pain associated with HFSR.

HFSR is one of the most commonly observed adverse events in patients treated with sorafenib. According to a meta-analysis of clinical research to date, 42% of patients administered sorafenib developed HFSR, and grade 3 HFSR was observed in 9% of all patients [8]. However, its clinical course is unknown and the frequency and time course of grade 1 HFSR developing into grade 2 or 3 was unclear. In the present prospective study, HFSR progressed from grade 1 to 2 or 3 in ~70% of patients treated with sorafenib and using only common topical 10% urea cream for HFSR treatment.

The importance of an effective treatment of HFSR has been recognized, and studies have been conducted, but no treatment has been proven to be effective. One reason is the lack of understanding regarding the pathogenic mechanism of HFSR. Two mechanisms have been reported for the development of sorafenib-related HFSR [9]: (i) damaged vascular integrity because of the dual inhibition of vascular endothelial growth factor receptor-2 (VEGFR-2) and platelet-derived growth factor(PDGF), and (ii) keratinocyte injury resulting from sorafenib-induced inhibition of c-kit or Raf kinase [10, 11]. It is unclear which of these mechanisms predominate. Lipworth et al. [12] recently reported that irregular epidermal hyperplasia with dermal edema, vascular dilatation, and a mononuclear superficial perivascular infiltrate were histologically observed in the lesions of...
sorafenib-associated HFSR. This suggests that tissue hypoxia induced by vascular damage and tissue inflammation may contribute to the development of sorafenib-associated HFSR. Furthermore, HFSR has been shown to be more severe at pressure points. It is here that we noted the similarity between sorafenib-associated HFSR and pressure ulcers. Circulatory disturbances due to chronic external forces and functional disorders of the lymphatic system are also considered to be involved in the pathogenesis of pressure ulcers [13]. Therefore, we considered that treatments of pressure ulcers were promising candidates to treat HFSR.

Many treatments have been attempted for pressure ulcers, and a hydrocolloid dressing containing ceramide with a low-friction external surface as a skin protection material has recently been widely used in Japan. The dressing has several potentially beneficial characteristics in that it contains ceramide, which has a strong skin-protecting effect, it reduces skin friction, buffers pH, shields the skin from bacteria, and acts as a cushion [7]. We therefore evaluated whether or not applying this dressing early after the onset of HFSR could prevent its exacerbation. Indeed, the frequency of the exacerbated HFSR was significantly lower with this treatment than with 10% urea cream. HFSR on the palms was also evaluated as a control because HFSR may be affected by constitutions and genetic factors. No difference in HFSR of the palms, which were not treated with either agent, was observed between the groups. This suggests that the dressing was effective to prevent HFSR progression on the soles of the feet.

Topical treatments with ointments containing urea or steroids have been used for the management of HFSR, but their true effectiveness is unclear. Lacouture et al. [14] reported that 40% urea cream singly plus 0.1% tazarotene cream or 5% fluorouracil cream was effective in 7 of 12 patients. However, the number of patients was small, and there were no controls in their study. The present study, on the other hand, further investigated treatment effectiveness by comparing QOL between the two groups using a self-administered questionnaire based on VAS. We showed that pain was lessened in the patients who were used the dressing compared with those who applied the urea cream.

Reducing the dose of sorafenib for 7–28 days has been recommended if the patient develops grade 2 HFSR, and discontinuing its administration for 7 days has been recommended if grade 3 HFSR develops [15, 16]. The effects of various HFSR treatments on the duration of sorafenib discontinuation were unclear. In the present study, the mean period of sorafenib withdrawal due to HFSR was 2 days in the group using the dressing and 5 days in the 10% urea cream group. Since avoiding any period of sorafenib discontinuation is important to obtain its maximum therapeutic effect, further improvements in the ceramide-containing dressing are also necessary.

The greatest limitation in this study was that the number of subjects assessed was smaller than planned, which led to a marked impairment in the statistical power. Another problem was the brevity of the observation period, which was only 1 month. Therefore, while a hydrocolloid dressing containing ceramide with a low-friction external surface was shown to be effective for a 1-month period, its long-term efficacy was not evaluated. However, it is important that this dressing prevented the exacerbation of HFSR even over short periods of time. This study also focused on sorafenib-associated HFSR only. As HFSR can be induced by other VEGF-tyrosine kinase inhibitors, such as sunitinib and pazopanib [15, 17], it is necessary to examine whether this treatment is also effective against HFSR associated with those drugs.

The present study revealed that a hydrocolloid dressing containing ceramide with a low-friction external surface was effective for controlling sorafenib-associated HFSR. Sorafenib is currently used for the treatment of liver and kidney cancers [18], but with the widening of its indications, it will be necessary to gain additional understanding of the adverse events associated with it, particularly HFSR, and further develop effective prevention methods.

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Stepping from traditional to integrative medicine: perspectives of Israeli-Arab patients on complementary medicine’s role in cancer care

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Background: Limited research is available on the perspectives of patients with cancer regarding integration of complementary medicine (CM) in conventional supportive cancer care. The purpose of this study was to explore patients’ perspectives concerning CM integration within conventional oncology settings.

Patients and methods: A 27-item questionnaire was constructed and administered to a convenient sample of Arab patients receiving cancer care in three oncology centers in northern Israel.